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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02025024.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 02025024.7
Demande no:

Anmeldetag:
Date of filing: 11.11.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Bayer Aktiengesellschaft

51368 Leverkusen
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Aryl or heteroaryl amino alkane derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/ Classification internationale des brevets:

C07D239/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

Aryl or heteroaryl amino alkane derivatives

Detailed Description of Invention

Technical Field

The present invention relates to an aryl or heteroaryl amino alkane derivatives which are useful as an active ingredient of pharmaceutical preparations. The aryl or heteroaryl amino alkane derivatives of the present invention have PGI2 [prostaglandin I2, prostacyclin] antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with PGI2 activity.

More specifically the aryl or heteroaryl amino alkane derivatives of the present invention are useful for treatment and prophylaxis of urological diseases or disorders.

The compounds of the present invention are also useful for treatment of pain; hypotension; hemophilia and hemorrhage; inflammation; respiratory states from allergies or asthma, since the diseases also relate to PGI2.

BACKGROUND ART

Prostaglandins (or prostanoids, PGs) are a group of bioactive lipid mediators generated from membrane phospholipids. They are formed from 20-carbon essential fatty acids containing 3, 4, or 5 double bonds, and carry a cyclopentane ring. They are divided into 6 main classes (D, E, F, G, H or I) by the cyclopentane ring structure. The main classes are further subdivided by subscripts 1, 2, or 3, reflecting their fatty acid precursors. PGI2 is a member of prostanoids, and it has a double ring structure and is derived from arachidonic acid. The receptor for PGI2 is a seven transmembrane G-protein coupled receptor, called IP. IP couples at least to Gs-type G-protein, and activates adenylate cyclase and phospholipase C. The expression of IP

is demonstrated in aorta, coronary/pulmonary/cerebral arteries, platelets, lung, and dorsal root ganglions in addition to several other tissues.

One of the well-known actions of PGI2 is for blood vessels to cause vasodilation and hypotension. Especially in septic shock, PGI2 is produced and participate in the induction of systemic hypotension (G.D. Bottoms et al, Am J Vet Res 1982, 43(6), 999-1002). Therefore, IP receptor antagonists may prevent hypotension associated with septic shock.

Another well-known action of PGI2 is for platelets to suppress aggregation. In the IP receptor knock out mice, $FeCl_3$-induced thrombosis formation was enhanced compared to that in wild type mice (T. Murata et al, Nature 1997, 388, 678- 682.), confirming the involvement of IP receptor in the platelet inhibition. Therefore, IP receptor antagonists may enhance the platelet activation and suppress excessive bleeding such as, but not limited to, hemophilia and hemorrhage.

PGI2 also participate in the inflammation. In the inflamed tissue, various inflammatory mediators, including prostaglandins, are produced. PGI2 is also generated and induces vasodilation to increase blood flow. This enhances vascular permeability, edema formation and leukocyte inflammation in the inflamed region (T. Murata et al, Nature 1997, 388, 678- 682.). Therefore, PGI2 receptor antagonists may be efficacious for the treatment of inflammation.

PGI2 may be involved in the pathogenesis of respiratory allergy or asthma. It is spontaneously generated and the major prostaglandin in human lung, and the appropriate antigen challenge increases PGI2 production (E.S. Schulman et al, J Appl Physiol 1982; 53(3), 589-595.). Therefore, IP antagonists may have a utility for the treatment of those respiratory diseases.

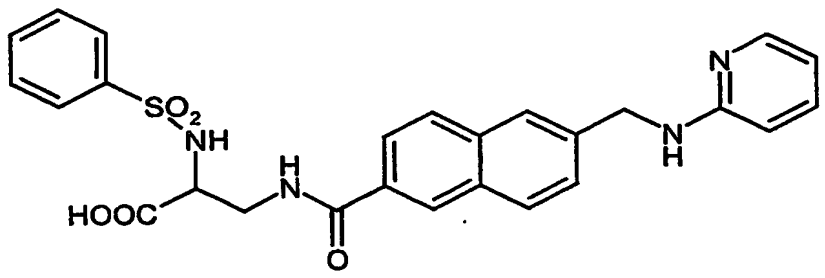
In addition, an important role of IP receptor in the induction of hyperalgesia has been clearly shown by IP receptor knockout mice (T. Murata et al., Nature 1997, 388,

678-682.). Injection of acetic acid into the peritoneal cavity induced production of PGI2. This PGI2 is considered to bind to IP receptor on sensory neurons. As IP receptor couples to the activation of both adenylate cyclase and phospholipase C, cAMP-dependent protein kinase (PKA) and protein kinase C (PKC) are activated. PKA and PKC are known to modulate ion channels on sensory neurons such as VR1, P2X3, and TTX-R. As a result, PGI2 sensitizes sensory neurons to enhance the release of neurotransmitters. Hence, acetic acid injection induces nociceptive response (writhing) in mice. This acetic acid-induced writhing was greatly reduced in PGI2 receptor-null mice as the same level as indomethacin-treated wild type mice. Several other in vivo hyperalgesia studies in rodents and in vitro studies further support that PGI2 plays a major role in the induction of hyperalgesia and that PGI2 acts as important modulator of sensory neurons (K. Bley et al, Trends in Pharmacological Sciences 1998, 19(4), 141-147.). Therefore, PGI2 receptor antagonists may be useful for the treatment of pain.

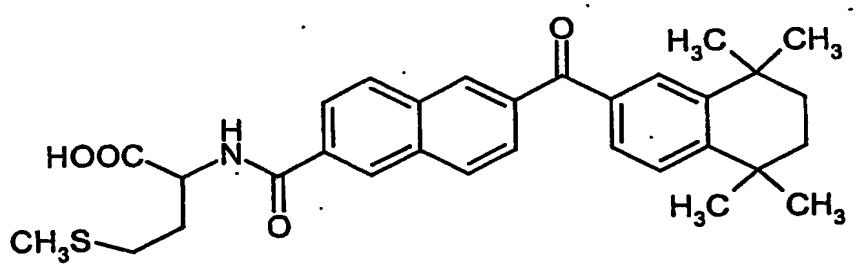
Sensory neurons play very important roles not only in the pain sensation but also in the sensation of bladder distension. In normal subjects, A-delta sensory fibers are considered to play a major role to sense the bladder distention. However, in disease conditions of overactive bladder by, but not limited to, spinal cord injury, cystitis, Parkinson's disease, multiple sclerosis, previous cerebrovascular accident, and bladder outlet obstruction (BOO) caused by benign prostate hyperplasia (BPH), the sensitivity of C-fiber sensory neurons is upregulated and they contribute to the induction of the lower urinary tract symptoms. Treatment of overactive bladder patients with intravesical injection of capsaicin or its potent analog, resiniferatoxin, both of which desensitize VR1-positive C-fiber afferent neurons innervating the bladder, has been shown to be efficacious in several clinical trials (C. Silva et al, Eur Urol. 2000, 38(4), 444-452.). Therefore, C-fiber sensory neurons play an important role in the pathology of overactive bladder. PGI2 is generated locally in the bladder and it is the major prostaglandin released from the human bladder. In a rabbit BOO model, a stable metabolite of PGI2 was reported to be increased in BOO bladder (JM. Masick et al, Prostaglandins Other Lipid Mediat. 2001, 66(3), 211-219.).

Hence, PGI2 from disease bladder sensitizes C-fiber sensory neurons, and as a result, it may induce symptoms of overactive bladder. Therefore, antagonists of PGI2 receptor are expected to be useful in the treatment of overactive bladder and related urinary disorders.

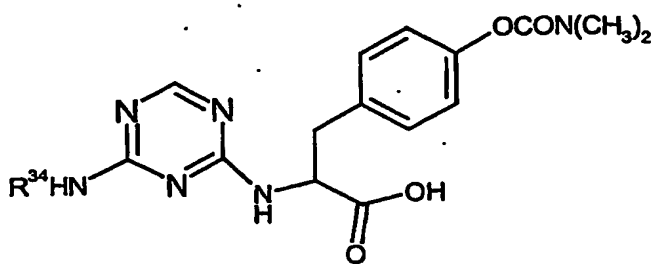
WO 98/44797 discloses integrin antagonists and farnesyl protein transferase inhibitors represented by the general formula:



EP-A-220118 discloses pharmaceutical composition intended for the treatment of dermatological, respiratory and ophthalmological conditions represented by the general formula:



WO 00/43369 discloses pharmaceutical composition intended for the treatment of immune or inflammatory disorders represented by the general formula:



wherein R^{34} is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl.

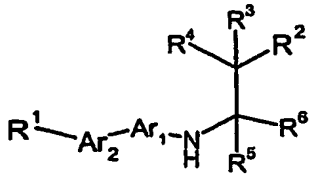
However, none of the references and other reference discloses aryl or heteroaryl amino alkane derivatives having PGI2 antagonistic activity.

The development of a compound which has effective PGI2 antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with PGI2 activity, has been desired.

Summary of the invention

As the result of extensive studies on chemical modification of aryl or heteroaryl amino alkane derivatives, the present inventors have found that the compounds of the structure related to the present invention have unexpectedly excellent PGI2 and/or antagonistic activity. The present invention has been accomplished based on these findings.

This invention is to provide a novel aryl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

wherein

Ar_1 and Ar_2 independently represent phenyl, or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally having one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, C_{1-6} alkyl optionally substituted -mono, -di or -tri halogen, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, aryl and heteroaryl;

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NR^{12}R^{13}$, or $-CHR^{14}R^{15}$,

wherein

R^{11} represents (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, or (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl;

R^{12} and R^{13} independently represent hydrogen, (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl,

or

R^{12} and R^{13} together form with the nitrogen atom, 5-7 membered saturated hetero ring optionally interrupted by O or NH;

R^{14} and R^{15} independently represent hydrogen, aryloxy, heteroaryloxy, (C_{1-6}) alkyl optionally substituted by aryl, heteroaryl, aryloxy, or heteroaryloxy, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by

aryl or heteroaryl, aryl substituted (C_{1-6}) alkoxy(C_{1-6}) alkylene, or heteroaryl substituted (C_{1-6}) alkoxy(C_{1-6}) alkylene,

or

R^{14} and R^{15} together form with the CH, (C_{3-8})cycloalkyl optionally interrupted by NH, or O,

or

R^{14} and R^{15} together form with the CH, phenyl optionally substituted by hydroxy, halogen or (C_{1-6}) alkyl;

R^2 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, di(C_{1-6}) alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, and di(C_{1-6}) alkylamino;

R^3 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, di(C_{1-6}) alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, and di(C_{1-6}) alkylamino;

R^4 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen,

hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^5 represents hydrogen, halogen, cyano, or C_{1-6} alkyl optionally substituted -mono, -di or -tri halogen; and

R^6 represents carboxy or tetrazolyl.

The compounds of the present invention surprisingly show excellent PGI2 antagonistic activity. They are, therefore, suitable for the production of medicament or medical composition, which may be useful to treat PGI2 related diseases.

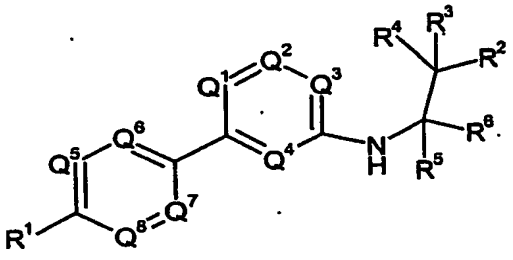
More specifically, since the aryl or heteroaryl amino alkane derivatives of the present invention antagonize PGI2, they are useful for treatment and prophylaxis of urological diseases or disorder.

The compounds of the present invention are also useful for treatment of urological diseases or disorders. Such diseases or disorders include bladder outlet obstruction, overactive bladder, urinary incontinence, detrusor hyper-reflexia, detrusor instability, reduced bladder capacity, frequency of micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benighn prostatic hypertrophy (BPH), prostatitis, urinary frequency, nocturia, urinary urgency, pelvic hypersensitivity,

urethritis, pelvic pain syndrome, prostatodynia, cystitis, or idiophatic bladder hypersensitivity.

The compounds of the present invention are also useful for treatment of pain including, but not limited to inflammatory pain, neuropathic pain, acute pain, chronic pain, dental pain, premenstrual pain, visceral pain, headaches, and the like; hypotension; hemophilia and hemorrhage; inflammation; respiratory states from allergies or asthma, since the diseases also relate to PGI2.

In another embodiment, the present invention provides an aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:



(I-i)

wherein

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 independently represent CH or N;

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NR^{12}R^{13}$, or $-CHR^{14}R^{15}$,

wherein

R^{11} represents (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, or (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl;

R^{12} and R^{13} independently represent hydrogen, (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl,

or

R^{12} and R^{13} together form with the nitrogen atom, 5-7 membered saturated hetero ring optionally interrupted by O or NH;

R^{14} and R^{15} independently represent hydrogen, aryloxy, heteroaryloxy, (C_{1-6}) alkyl optionally substituted by aryl, heteroaryl, aryloxy, or heteroaryloxy, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl, aryl substituted (C_{1-6}) alkoxy(C_{1-6}) alkylene, or heteroaryl substituted (C_{1-6}) alkoxy(C_{1-6}) alkylene,

or

R^{14} and R^{15} together form with the CH, (C_{3-8})cycloalkyl optionally interrupted by NH, or O,

or

R^{14} and R^{15} together form with the CH, phenyl optionally substituted by hydroxy, halogen or (C_{1-6})alkyl;

R^2 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^3 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^4 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^5 represents hydrogen, hydroxy, cyano, or C_{1-6} alkyl optionally substituted -mono, -di or -tri halogen; and

R^6 represents carboxy or tetrazolyl.

Yet another embodiment of the compounds of formula (I-i) are those wherein:

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^6 represents carboxy.

Another embodiment of the compounds of formula (I-i) is those wherein:
Q^3 and Q^4 represent N;

Q^1, Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^6 represents carboxy.

Another embodiment of the compounds of formula (I-i) is those wherein:

Q^1 and Q^4 represent N;

Q^2, Q^3, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^6 represents carboxy.

Another embodiment of the compounds of formula (I-i) is those wherein:

Q^1 , $Q^2$and Q^3 represent CH.

Another embodiment of the compounds of formula (I-i) is those wherein:

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^6 represents carboxy.

Another embodiment of the compounds of formula (I-i) is those wherein:

Q^1, Q^3 and Q^8 represent N;

Q^2, Q^4, Q^5, Q^6 and Q^7 represent CH; and

R^6 represents carboxy.

Another embodiment of the compounds of formula (I-i) is those wherein:

Q^3, Q^4 and Q^8 represent N;

Q^1, Q^2, Q^5, Q^6 and Q^7 represent CH; and

R^6 represents carboxy.

Further embodiment of the compounds of formula (I) or (I-i) are those wherein

R^1 represents aryl(C_{1-6})alkoxy, aryl(C_{1-6})alkoxy(C_{1-6})alkylene or aryl-oxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or aryl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino.

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

Yet further embodiment of the compounds of formula (I) or (I-i) are those wherein

R^1 represents phenyl(C_{1-6})alkoxy, phenyl(C_{1-6})alkoxy(C_{1-6})alkylene or phenoxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

More preferably, said aryl or heteroaryl amino alkane derivatives of the formula (I) is selected from the group consisting of:

N-{4-[4-(benzyloxy)phenyl]-2-pyrimidinyl}phenylalanine;
N-{6-[4-(Benzyloxy)phenyl]-4-pyrimidinyl}phenylalanine;
N-{4-[4-(Benzyloxy)phenyl]-2-pyrimidinyl}phenylalanine;
N-{2-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalanine; and

N-[4'-(Benzyloxy)-1,1'-biphenyl-3-yl]phenylalanine.

Further, the present invention provides a medicament, which includes one of the compounds, described above and optionally pharmaceutically acceptable excipients.

The Alkyl per se and "alk" and "alkyl" in alkoxy, alkanoyl, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

Aryl per se represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, illustratively and preferably representing phenyl, naphthyl and phenanthrenyl.

Heteroaryl per se represents an aromatic mono- or bicyclic radical having generally 5 to 10 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 hetero atoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl,

pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

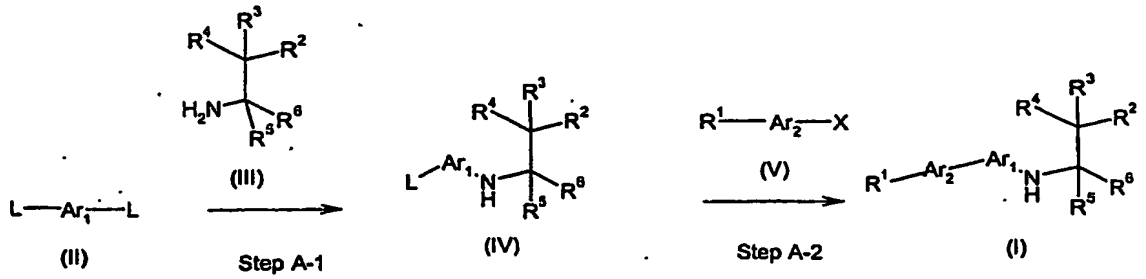
5- and 6-membered heteroaromatic rings illustratively and preferably represent tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, 1,2,4-triazine and 1,3,5-triazine.

EMBODIMENT OF THE INVENTION

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by combining various known methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis. (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by the Method [A], [B] or [C]below.

Method [A]



The compound of the formula (I) (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4, R^5 and R^6 are the same as defined above) can be obtained in two steps;

Step A-1: the compound of the formula (IV) (wherein Ar_1, R^2, R^3, R^4, R^5 and R^6 are the same as defined above and L represents a leaving group including, for example, halogen atom such as chlorine, bromine, or iodine atom; and C_{1-4} alkylsulfonyloxy group, e.g., trifluoromethanesulfonyloxy, methanesulfonyloxy and the like) can be obtained by the reaction of the compound of the formula (II) (wherein Ar_1 and L are the same as defined) with the compound of the formula (III) (wherein R^2, R^3, R^4, R^5 and R^6 are the same as defined above).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction can be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, triethylamine and N,N-diisopropyl-ethylamine, dimethylaniline, diethylaniline, and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Step A-2: The compound of the formula (I) (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4, R^5 and R^6 are the same as defined above) can be obtained by the reaction of the compound of the formula (IV) (wherein Ar_1, L, R^2, R^3, R^4, R^5 and R^6 are the same as defined above) with the compound of the formula (V) (wherein Ar_2 and R^1 are the same as defined above and X represents metal group including, for instance, organoborane

group such as boronic acid and di-methoxy boryl; organostannyl group such as tributyl stannyl, and the like.) in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium.

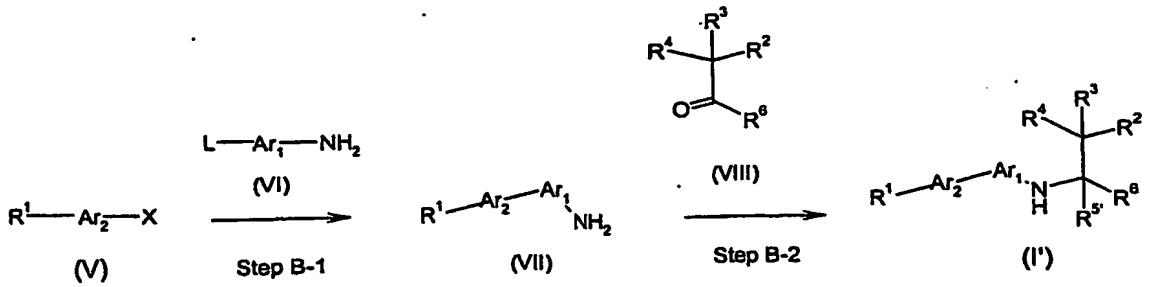
The reaction can be advantageously carried out in the presence of a base including, for instance, cesium carbonate, sodium carbonate and potassium carbonate, and the like.

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The compound of the formula (II), (III), and (V) are commercially available or can be prepared by the use of known techniques.

Method [B]



The compound of the formula (I') (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4 and R^6 are the same as defined above and $R^{5'}$ represents hydrogen) can be obtained by in two steps;

Step B-1 : The compound of the formula (VII) (wherein Ar_1, Ar_2 and R^1 are the same as defined above) can be obtained by the reaction of the compound of the formula (V) (wherein X, Ar_2 and R^1 are the same as defined above) with the compound of the formula (VI) (wherein Ar_1 and L are the same as defined above) in the same manner decribed in Step A-2 of Method [A] for the preparation of the compound of the formula (I).

Step B-2 : The compound of the formula (I') (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4 and R^6 are the same as defined above and $R^{5'}$ represents hydrogen) can be obtained by the reaction of the compound of the formula (VII) (wherein Ar_1, Ar_2 and R^1 are the same as defined above) with the compound of the formula (VIII) (wherein R^2, R^3, R^4 and R^6 are the same as defined above) in the presence of reducing agent, for instance, such as sodium triacetoxyborohydride or sodium cyanoborohydride, and the like.

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; organic acid such as acetic acid; water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The compound of the formula (V), (VI) and (VIII) are commercially available or can be prepared by the use of known techniques.

Method [C]

(IX) (I'')

The compound of the formula (I'') (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4,and R^5 are the same as defined above) can be obtained by the hydrolysis of the compound of formula (IX) (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4,and R^5 are the same as defined above, and Y represents C_{1-6} alkyl).

The reaction can be advantageously carried out in the presence of a base including, for instance, alkali metal hydroxide such as sodium hydroxide, lithium hydroxide and potassium hydroxide; and others.

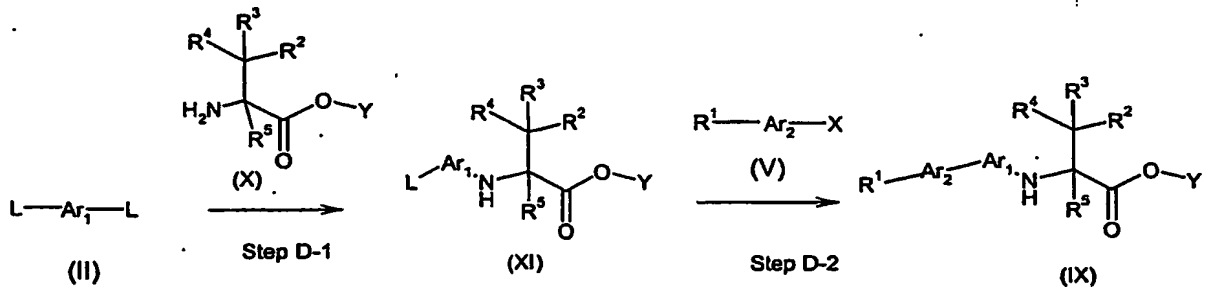
The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; water, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Preparation of the compound of the formula (IX)

The compound of the formula (IX) of the present invention can be, but not limited to be, prepared by Method [D] or [E] below.

Method [D]



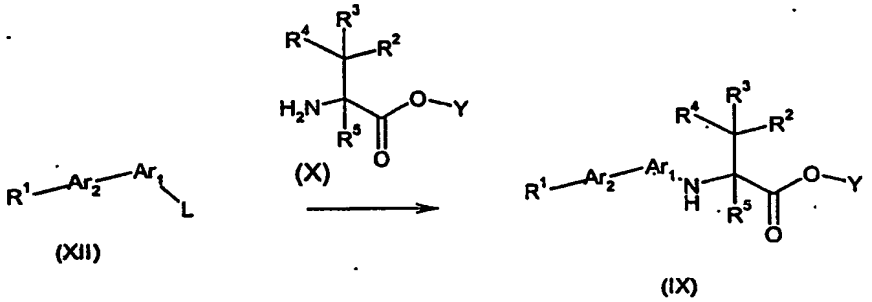
The compound of the formula (IX) (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4, R^5 and Y are the same as defined above) can be obtained in two steps;

Step D-1: the compound of the formula (XI) (wherein Ar_1, L, R^2, R^3, R^4, R^5 and Y are the same as defined above) can be obtained by the reaction of the compound of the formula (II) (wherein Ar_1 and L are the same as defined) with the compound of the formula (X) (wherein R^2, R^3, R^4, R^5 and Y are the same as defined above) in the same manner decribed in Step A-1 of Method [A] for the preparation of the compound of the formula (IV).

Step D-2: the compound of the formula (IX) (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4, R^5 and Y are the same as defined above) can be obtained by the reaction of the compound of the formula (XI) (wherein Ar_1, L, R^2, R^3, R^4, R^5 and Y are the same as defined above) with the compound of the formula (V) (wherein Ar_2, R^1 and X are the same as defined) in the same manner decribed in Step A-2 of Method [A] for the preparation of the compound of the formula (I).

The compound of the formula (II), (V) and (X) are commercially available or can be prepared by the use of known techniques.

Method [E]



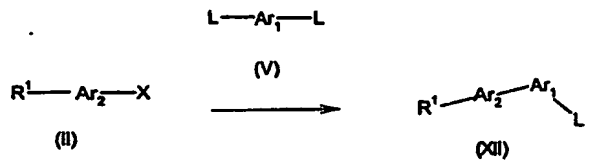
(XII) (X) (IX)

The compound of the formula (IX) (wherein Ar_1, Ar_2, R^1, R^2, R^3, R^4, R^5 and Y are the same as defined above) can be obtained by the reaction of the compound of formula (XII) (wherein Ar_1, Ar_2, R^1 and L are the same as defined above) with the compound of the formula (X) (wherein R^2, R^3, R^4, R^5 and Y are the same as defined above) in the same manner decribed in Step A-1 of Method [A] for the preparation of the compound of the formula (IV).

Preparation of the compound of the formula (XII)

The compound of the formula (XII) of the present invention can be, but not limited to be, prepared by Method [F] below.

Method [F]



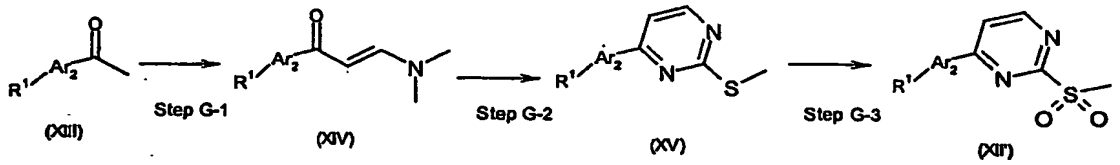
(II) (V) (XII)

The compound of formula (XII) (wherein Ar_1, Ar_2, R^1 and L are the same as defined above) can be prepared by the reaction of compound (II) (wherein Ar_2, R^1 and X are the same as defined) with the compound of the formula (V) (wherein Ar_1 and L are the same as defined) in the same manner decribed in Step A-2 of Method [A] for the preparation of the compound of the formula (I).

Preparation of the compound of the formula (XII')

The compound of formula (XII') (wherein Ar_2, R^1 and L are the same as defined above) can be, but not limited to be, prepared in three steps by Method [G].

Method [G]



(XIII) (XIV) (XV) (XII')

Step G-1 : The compound of the formula (XIV) (wherein Ar_2 and R^1 are the same as defined above) can be obtained by the reaction of the compound of formula (XIII) (wherein Ar_2 and R^1 are the same as defined above) with *N*-[tert-butoxy(dimethylamino)methyl]-N,N-dimethylamine.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 150°C.

The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Step G-2 : The compound of the formula (XV) (wherein Ar_2 and R^1 are the same as defined above) can be obtained by the reaction of the compound of formula (XIV) (wherein Ar_2 and R^1 are the same as defined above) with thiourea and successive treatment with methyl iodide.

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction can be advantageously carried out in the presence of a base including, for instance, alkali metal hydroxide such as, sodium hydroxide, lithium hydroxide and potassium hydroxide; and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Step G-3 : The compound of the formula (XII') (wherein Ar_2, and R^1 are the same as defined above) can be obtained by the oxidation reaction of the compound of formula (XV) (wherein Ar_2 and R^1 are the same as defined above) using oxidating agrent for instance, such as hydrogen peroxide, m-chloroperbenzoic acid, oxone, and the others. The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-

methylpyrrolidone; alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; water, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 150°C.

The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The compound of the formula (XIII), *N*-[tert-butoxy(dimethylamino)methyl]-N,N-dimethylamine and oxidating agent are commercially available or can be prepared by the use of known techniques.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, successively.

Acids to form salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal

hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring

agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxy-methyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01 mg/kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven

advantageous to administer quantities of about 0.001 to 100 mg/kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Examples

The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the meets and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Melting points are uncorrected. Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column (4.6 mm x 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate. Mass spectra were obtained using electrospray (ES) ionization techniques (micromass Platform LC). TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Great Britain, Tokyo kasei kogyo Co., Ltd., Japan, Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Great Britain, Merck KgaA, Germany, Kanto Chemical Co., Ltd. ^{1}H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ^{1}H) spectrometer or Brucker 500 UltraShieled™ (500 MHz for 1H) . Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations. s, d, t, q; m, and br refer to singlet, doblet, triplet, quartet, multiplet, and broad, respectively. The mass determinations were carried out by MAT95 (Finnigan MAT).

The effects of the present compounds were examined by the following assays and pharmacological tests.

[Measurement of the [^{3}H]-iloprost binding to HEL cells] (Assay 1)

A human erythloleukemia cell line, HEL 92.1.7, was purchased from American Type Culture Correction and maintained in RPMI-1640 medium (Gibco BRL) supplemented with 10% fetal calf serum (FCS), 2 mM glutamine, 4.5 g/L glucose, 10 mM Hepes, 1 mM sodium pyruvate, 100 U/ml penicillin, and 100 μg/ml streptomycin in a humidified 5% CO_2 atmosphere at 37°C. Cells were collected with centrifugation and washed with binding assay buffer (BAB: 50 mM Tris-HCl, 5 mM $MgCl_2$ (pH 7.5)). Cells were suspended at the density of 6.25 x 10^6 cells/ml in BAB, and one million cells in 160 μl aliquot of cell suspension were put in a well of 96 well plate (Falcon). Then, 20 μl of compound solution, 100 μM of iloprost (for non-specific binding), or buffer alone (total binding), diluted with 1% DMSO in BAB was added. Finally, another 20 μl containing [^{3}H]-iloprost (0.02 μCi, 0.5-1 pmol) in BAB was added and incubated at room temperature for 30 min with a gentle shaking. Cell suspension was then transferred to a well of MultiScreen plate with GF/C glass filters (Millipore) to harvest cells. Cells were washed twice with 200 μl of ice-cold BAB and the plate was kept at 55°C for 30 min to dry filters. The filter in the well was punched out to a counting tube and 2 ml of Ultima Gold XR (Packard) was added. [^{3}H]-radio activity in the filter was measured by a liquid scintillation counter (Beckman, USA).

[Iloprost-induced cAMP production assay in HEL cells] (Assay 2)

HEL cells were collected with centrifugation and washed with cAMP assay buffer (CAB: Hank's balanced salt solution, 17 mM Hepes, 0.1% bovine serum albumin, 1 mM IBMX, 0.4% DMSO, and 1 mM L-ascorbic acid sodium salt (pH 7.4)). Cells were suspended at the density of 2.5 x 10^5 cells/ml in CAB, and twenty thousand cells in 80 μl aliquot of cell suspension were put in a well of 96 well plate (Falcon). Then, 10 μl of compound solution diluted with 1% DMSO in CAB or buffer alone was added. The plate was incubated at 37°C for 30 min. Then, another 10 μl containing 100 nM iloprost in CAB or buffer alone was added and further incubated

at 37°C for 30 min. cAMP content in the well was measured by a cAMP ELISA kit (Applied Biosystems, USA).

[Measurement of rhythmic bladder contraction in anesthetized rats]

(1) Animals

Female Sprague-Dawley rats (200~250 g / Charles River Japan) were used.

(2) Rhythmic bladder contraction in anesthetized rats

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.25 g/kg. The trachea was cannulated with a polyethylene tube (HIBIKI, No.8) to facilitate respiration; and a cannula (BECTON DICKINSON, PE-50) was placed in the left femoral vein for intravenous administration of testing compounds. The abdomen was opened through a midline incision, and after both ureters were cut, a water-filled balloon (about 1 ml capacity) was inserted through the apex of the bladder dome. The balloon was connected to a pressure transducer onto a polygraph. Rhythmic bladder contraction was elicited by raising up intravesical pressure to approximately 15 cm H_2O. After the rhythmic bladder contraction was stable, a testing compound was administered intravenously. Activity was estimated by measuring disappearance time and amplitude of the rhythmic bladder contraction. The effect on amplitude of bladder contractions was expressed as a percent suppression of the amplitude of those after the disappearance was recovered. Experimental values were expressed as the mean±S.E.M. The testing compounds–mediated inhibition of the rhythmic bladder contraction was evaluated using Student's t-test. A probability level less than 5% was accepted as significant difference.

Results of PGI2 receptor binding/cAMP is shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase

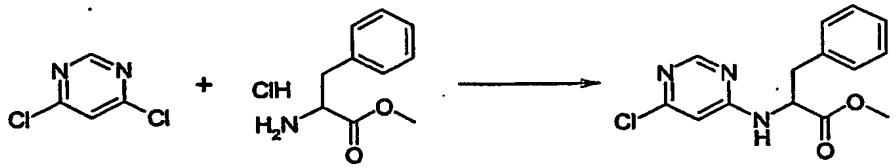
synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in three classes of activity as follows:

IC_{50} = A <0.1 μM ≤B <1 μM ≤ C.

The compounds of the present invention also show excellent selectivity, and strong activity in vivo assays.

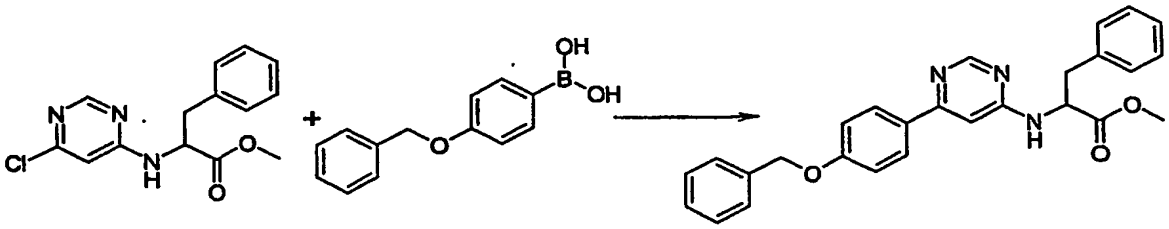
Example 1-1:

Methyl *N*-(6-chloro-4-pyrimidinyl)phenylalaninate



To a mixture of 4,6-dichloropyrimidine (0.500 g, 3.356 mmol), DL-phenylalanine methyl ester hydrochloride (0.796 g, 3.692 mmol) and ethanol (15 mL) was added *N,N*-diisopropylethylamine (1.228 mL, 7.048 mmol), and the mixture was stirred at reflux for 2 hours. After cooled to room temperature, the mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel (hexane: ethyl acetate, 3:1) to give methyl *N*-(6-chloro-4-pyrimidinyl)phenylalaninate (0.497 g, 51%) as a colorless oil.

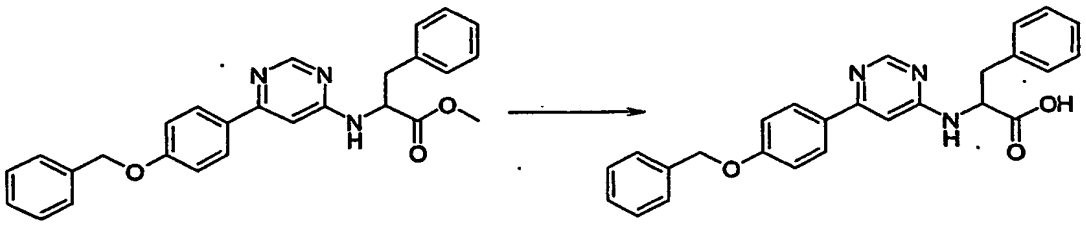
Methyl *N*-{6-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate



To a mixture of methyl *N*-(6-chloro-4-pyrimidinyl)phenylalaninate (0.192 g, 0.658 mmol), 4-(benzyloxy)phenylboronic acid (0.150 g, 0.658 mmol) and DMF

(3 mL) under an argon atmosphere was added 2N sodium carbonate aqueous solution (0.975 mL, 1.95 mmol) followed by tetrakis(triphenylphosphine)palladium (0.038 g, 0.033 mmol). The mixture was stirred at 100 °C overnight. After cooled to room temperature, the mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel (hexane: ethyl acetate, 2:1) to give methyl *N*-{6-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate (0.028 g, 10%) as a colorless oil.

N-{6-[4-(Benzyloxy)phenyl]-4-pyrimidinyl}phenylalanine



To a solution of methyl *N*-{6-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate (0.028 g, 0.064 mmol) in methanol (0.2 mL), water (0.2 mL) and tetrahydrofuran (0.2 mL), was added lithium hydroxide monohydrate (0.005g, 0.1mmol) and the mixture was stirred at room temperature for 2 hours. The mixture was diluted with water (5 mL), and the aqueous phase was washed twice with ether. The separated aqueous phase was neutralized with 1N hydrochloric acid solution (0.1 mL) and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was triturated with ether and dried under reduced pressure to give *N*-{6-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalanine (0.016 g, 59%) as a white solid.

Melting point: 175-178 °C

Molecular weight: 425.49

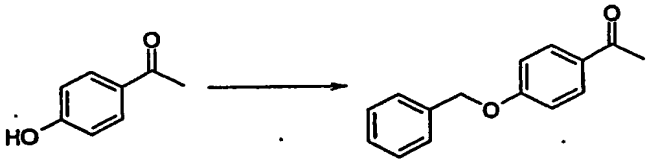
Mass spectrometry: 426 $(M + H)^+$

In vitro activity grade: A

^{1}H-NMR (500 MHz, DMSO): δ 3.00 (1H, dd, J = 9.5, 13.9 Hz), 3.19 (1H, dd, J = 4.6, 13.9 Hz), 4.77 (1H, br), 5.17 (2H, s), 6.98 (1H, br s), 7.11 (2H, d, J = 9.0 Hz), 7.18-7.21 (1H, m), 7.25-7.29 (4H, m), 7.34 (1H, t, J = 7.3 Hz), 7.40 (2H, t, J = 7.1 Hz), 7.47 (2H, d, J = 7.1 Hz), 7.61 (1H, br), 7.93 (2H, d, J = 8.0 Hz), 8.43 (1H, s), 12.74 (1H, br s).

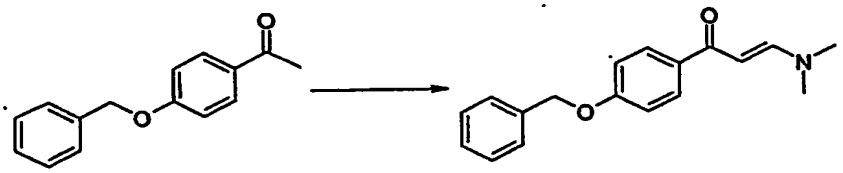
Example 2-1:

1-[4-(Benzyloxy)phenyl]ethanone:



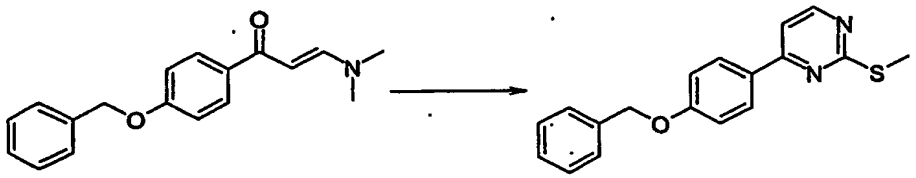
To a solution of 1-(4-hydroxyphenyl)ethanone (2.0 g, 14.69 mmol) and benzyl-chloride (2.23 g, 17.63 mmol) in DMF (40 mL) was added potassium carbonate (2.64 g, 19.10 mmol) and sodium iodide (0.22 g, 1.47 mmol), and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The separated organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residual solid was triturated with diisopropylether to give 1-[4-(benzyloxy)phenyl]ethanone (2.81 g, 85 %) as yellowish granules.

(2E)-1-[4-(Benzyloxy)phenyl]-3-(dimethylamino)-2-propen-1-one:



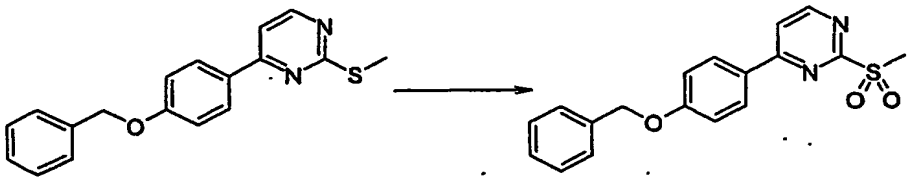
A mixture of 1-[4-(benzyloxy)phenyl]ethanone (2.0 g, 8.84 mmol) and *N*-[tert-butoxy(dimethylamino)methyl]-N,N-dimethylamine (2.31 g, 13.26 mmol) in toluene (12 mL) was stirred under reflux for 3 hours. The volatiles were removed by evaporation and the residual solid was triturated with diisopropylether to give *(2E)*-1-[4-(benzyloxy)phenyl]-3-(dimethylamino)-2-propen-1-one (2.51 g, quantitative) as a yellow powder.

4-[4-(Benzyloxy)phenyl]-2-(methylsulfanyl)pyrimidine:



To a solution of *(2E)*-1-[4-(benzyloxy)phenyl]-3-(dimethylamino)-2-propen-1-one (2.51 g, 9.39 mmol) and thiourea (1.43 g, 18.78 mmol) in ethanol (25 ml) was added portionwise sodium ethoxide (1.49 g, 21.87 mmol), and the mixture was stirred at 70°C for 2 hours. After the mixture being cooled, iodomethane (6.62 g, 46.94 mmol) was added, and the stirring was continued overnight. The mixture was filtered to remove the precipitate, which was rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica-gel (n-hexane:ethyl acetate, 7:1 - 3:1) to give 4-[4-(benzyloxy)phenyl]-2-(methylsulfanyl)pyrimidine (2.47 g, 85 %) as a slightly yellow solid.

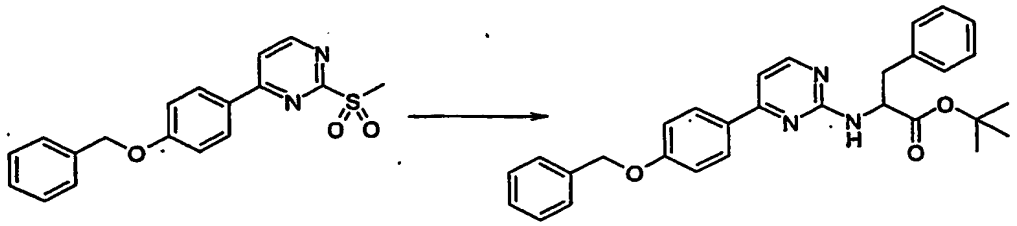
4-[4-(Benzyloxy)phenyl]-2-(methylsulfonyl)pyrimidine:



To a cold (0 °C) solution of 4-[4-(benzyloxy)phenyl]-2-(methylsulfanyl)pyrimidine (0.50 g, 1.62 mmol) in dichloromethane (6.0 mL) was added m-chloroperbenzoic acid (75 %, 0.75 g, 3.24 mmol), and the mixture was stirred for 4 hours. The mixture was poured into a mixture of 5 % aqueous sodium thiosulfate and dichloromethane. The organic phase was separated, washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a crude 4-[4-(benzyloxy)phenyl]-2-(methylsulfonyl)pyrimidine

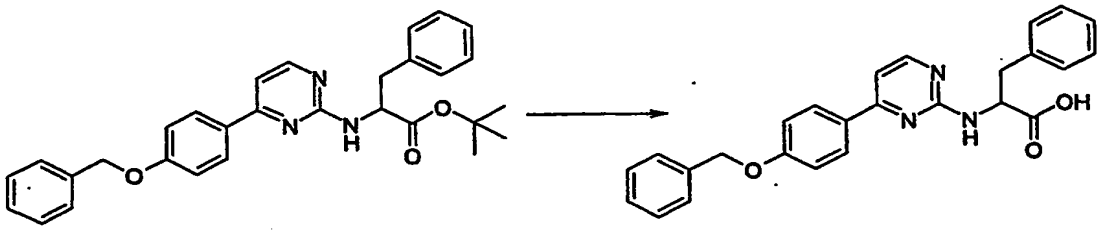
(0.54 g, 98 %) as a yellowish solid, which was used for the next step without further purification.

tert-Butyl N-{4-[4-(benzyloxy)phenyl]-2-pyrimidinyl}phenylalaninate:



A mixture of 4-[4-(benzyloxy)phenyl]-2-(methylsulfonyl)pyrimidine (300 mg, 0.88 mmol) and DL-phenylalanine tert-butyl ester (585 mg, 2.64 mmol) was stirred at 120 °C overnight. After being cooled to room temperature, the mixture was purified by column chromatography on silica-gel (chloroform) to give *tert*-butyl N-{4-[4-(benzyloxy)phenyl]-2-pyrimidinyl}-phenylalaninate (260 mg, 61 %) as a yellowish solid.

N-{4-[4-(Benzyloxy)phenyl]-2-pyrimidinyl}phenylalanine:



To a solution of tert-butyl N-{4-[4-(benzyloxy)phenyl]-2-pyrimidinyl}-phenylalaninate (0.26 g, 0.54 mmol) in tetrahydrofuran (2.5 ml) and ethanol (2.5 ml) was added dropwise 1N LiOH (0.82 ml, 0.82 mmol) and the mixture was stirred under reflux overnight. After cooled to room temperature, the mixture was concentrated under reduced pressure. The residue was suspended in water and neutralized with 1N HCl (0.82 ml). The resultant precipitate was collected by filtration and washed successively with water and ethyl acetate to give N-{4-[4-(benzyloxy)phenyl]-2-pyrimidinyl}phenylalanine (0.117 g, 51 %) as a colorless powder.

Melting point: 174 °C

Molecular weight: 425.49

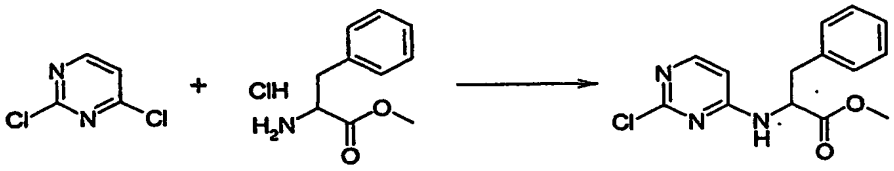
Mass spectrometry: 426 $(M + H)^+$

In vitro activity grade: A

^{1}H-NMR (500 MHz, CD3OD): δ 3.09 (1H, dd, J = 13.6, 7.3 Hz), 4.55 (1H, bs), 5.16 (2H, s), 6.98 (1H, d, J = 5.4 Hz), 7.07 (2H, dd, J = 6.9, 2.2 Hz), 7.09 (1H, t, J = 7.6 Hz), 7.17 (1H, t, J = 7.6 Hz), 7.24 (1H, d, J = 7.9 Hz), 7.31 (1H, t, J = 7.3 Hz), 7.38 (1H, t, J = 7.3 Hz), 7.46 (1H, d, J = 7.6 Hz), 8.05 (2H, bs), 8.14 (1H, bs).

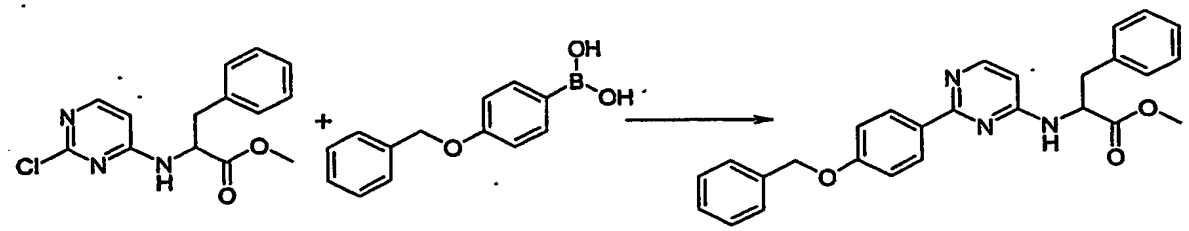
Example 3-1:

Methyl N-(2-chloro-4-pyrimidinyl)phenylalaninate



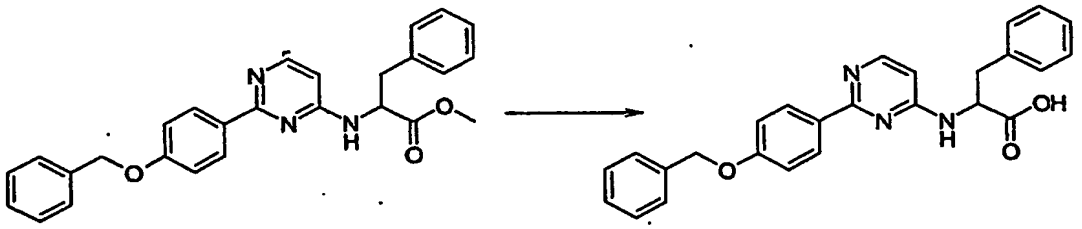
To a mixture of 2,4-dichloropyrimidine (0.800 g, 4.848 mmol), DL-phenylalanine methyl ester hydrochloride (1.098 g, 5.090 mmol) and ethanol (15 mL) was added *N,N*-diisopropylethylamine (1.773 mL, 10.18 mmol), and the mixture was stirred at reflux for 6 hours. After cooled to room temperature, the precipitate was removed filtration and washed with ethanol. The combined filtrates were concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel (hexane: ethyl acetate, 2:1) to give methyl N-(2-chloro-4-pyrimidinyl)phenylalaninate (1.020 g, 72%) as a colorless oil.

Methyl N-{2-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate:



To a mixture of methyl *N*-(2-chloro-4-pyrimidinyl)phenylalaninate (0.368 g, 1.261 mmol), 4-(benzyloxy)phenylboronic acid (0.316 g, 1.388 mmol) and DMF (5 mL)under an argon atmosphere was added a solution of sodium carbonate (0.414 g, 3.910 mmol) in water (2 mL) followed by tetrakis(triphenylphosphine)palladium (0.068 g, 0.059 mmol). The mixture was stirred at 95 °C overnight. After cooled to room temperature, the mixture was treated with 1N aqueous sodium hydroxide solution (2 mL) and stirred at room temperature for 2 hours. The mixture was diluted with water, and washed with ethyl acetate. The separated aqueous phase was neutralized by 1N aqueous hydrochloric acid solution. The resultant precipitate was collected by filtration, washed with water and dried under reduced pressure. The residue was dissolved in a mixture of methylene chloride (10 mL) and methanol (10 mL), and treated with a solution of diazomethane in ether, which was prepared from 1-methyl-3-nitro-1-nitrosoguanidine (0.5 g, 3.4 mmol), potassium hydroxide (6 g), water (9 g) and ether (25 mL). After being stirred for 1 hour, the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel (hexane: ethyl acetate, 2:1) to give methyl N-{2-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate (0.223 g, 40%) as a colorless oil.

N-{2-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalanine



To a solution of methyl *N*-{2-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate (0.251 g, 0.572 mmol) in methanol (2.0 mL), water (2.0 mL) and tetrahydrofuran (4.0 mL), was added lithium hydroxide monohydrate (0.030g, 0.715mmol) and the mixture was stirred at room temperature for 2 hours. The mixture was diluted with water (5 mL). The mixture was neutralized with 1N hydrochloric acid solution (0.715 mL). The rsultant crystal was collected by filtration, washed with water and

ether, and dried under reduced pressure to give *N*-{2-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalanine (0.178 g, 73%) as a white solid.

Melting point: 120-125 °C

Molecular weight: 425.49

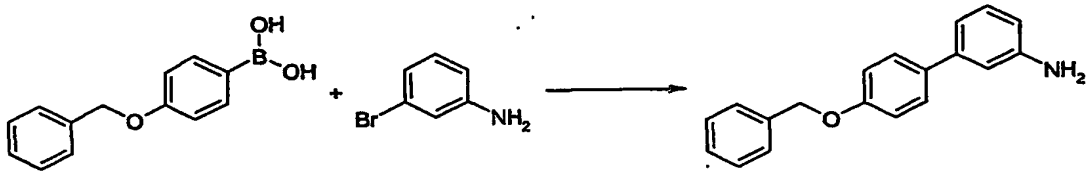
Mass spectrometry: 426 $(M + H)^+$

In vitro activity grade: A

^{1}H-NMR (500 MHz, DMSO): δ 3.04 (1H, dd, J = 9.3, 13.9 Hz), 3.19 (1H, dd, J = 5.0, 13.9 Hz), 4.75 (1H, br), 5.17 (2H, s), 6.45 (1H, d, J = 5.5 Hz), 7.07 (2H, d, J = 9.0 Hz), 7.19 (1H, dd, J = 6.9, 7.1 Hz), 7.25-7.36 (5H, m), 7.40 (2H, dd, J = 7.1, 7.7 Hz), 7.47 (2H, d, J = 7.1 Hz), 7.75 (1H, br), 8.11 (1H, d, J = 5.8 Hz), 8.23 (2H, d, J = 8.8 Hz), 12.66 (1H, br s).

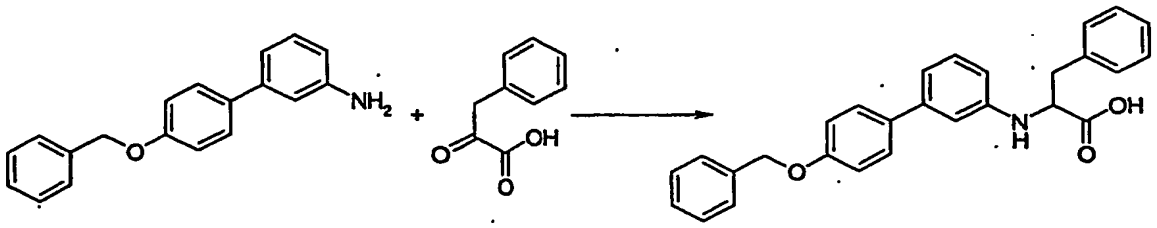
Example 4-1:

4'-(Benzyloxy)-1,1'-biphenyl-3-amine



To a mixture of 3-bromoaniline (90 mg, 0.53 mmol) and tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) in DMF (3 mL) was added a solution of sodium carbonate (209 mg, 1.97 mmol) in water (1 ml) folowed by (4-benzyloxyphenyl)boronic acid (150 mg, 0.66 mmol) in several portions. The mixture was stirred at 100 °C for 16 hours. After cooled to room temperature, the reaction mixture was diluted with water and extracted with chloroform. The separated organic phase was washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane: ethyl acetate, 2:1) to give 4'-(benzyloxy)-1,1'-biphenyl-3-amine (155 mg, 86%) as a white solid.

N-[4'-(Benzyloxy)-1,1'-biphenyl-3-yl]phenylalanine



To a mixture of 4'-(benzyloxy)-1,1'-biphenyl-3-amine (50 mg, 0.18 mmol) and phenylpyruvic acid (60 mg, 0.36 mmol) in acetic acid (1 mL) was added sodium sulfate (1.05 g, 1.82 mmol). The mixture was stirred at room temperature for 18 hours, and then added portionwise sodium triacetoxyborohydride (46 mg, 0.22 mmol). After stirred for 20 minutes, the reaction mixture was poured into water and extracted with chloroform. The separated organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane:ethyl acetate, 1:1) to give *N*-[4'-(benzyloxy)-1,1'-biphenyl-3-yl]phenylalanine (15 mg, 20%) as a white solid.

Melting point: 152-154 °C

Molecular weight: 423.51

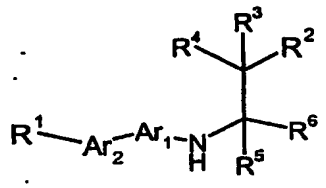
Mass spectrometry: 424 $(M + H)^+$

In vitro activity grade: A

^{1}H-NMR (500 MHz, DMSO-d6): δ 2.97 (1H, dd, J = 7.8, 12.8 Hz), 3.09 (1H, dd, J = 5.3, 12.8 Hz), 4.14 (1H, s), 5.14 (3H, s), 6.51 (1H, d, J = 8.2 Hz), 6.75 (1H, s), 7.06 (2H, d, J = 8.5 Hz), 7.09 (1H, d, J = 7.8 Hz), 7.18 (1H, t, J = 7.0 Hz), 7.26 (2H, t, J = 7.6 Hz), 7.30 (2H, d, J = 7.3 Hz), 7.34 (1H, d, J = 7.3 Hz), 7.40 (2H, d, J = 7.3 Hz), 7.46 (2H, d, J = 8.2 Hz), 7.47 (1H, d, J = 8.9 Hz).

Claims

(1) An aryl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

wherein

Ar_1 and Ar_2 independently represent phenyl, or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally having one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, C_{1-6} alkyl optionally substituted -mono, -di or -tri halogen, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, aryl and heteroaryl;

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NR^{12}R^{13}$, or $-CHR^{14}R^{15}$,

wherein

R^{11} represents (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, or (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl;

R^{12} and R^{13} independently represent hydrogen, (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkenyl optionally sub-

stituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl,

or

R^{12} and R^{13} together form with the nitrogen atom, 5-7 membered saturated hetero ring optionally interrupted by O or NH;

R^{14} and R^{15} independently represent hydrogen, aryloxy, heteroaryloxy, (C_{1-6}) alkyl optionally substituted by aryl, heteroaryl, aryloxy, or heteroaryloxy, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl, aryl substituted (C_{1-6}) alkoxy(C_{1-6}) alkylene, or heteroaryl substituted (C_{1-6}) alkoxy(C_{1-6}) alkylene,

or

R^{14} and R^{15} together form with the CH, (C_{3-8})cycloalkyl optionally interrupted by NH, or O,

or

R^{14} and R^{15} together form with the CH, phenyl optionally substituted by hydroxy, halogen or (C_{1-6}) alkyl;

R^2 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen,

hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^3 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^4 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, di(C_{1-6}) alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

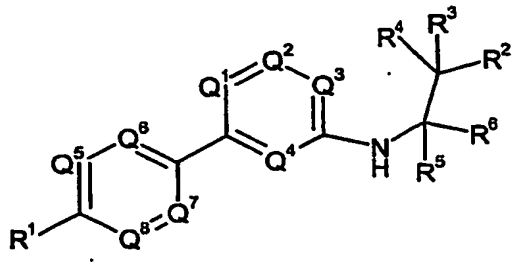
wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, and di(C_{1-6}) alkylamino;

R^5 represents hydrogen, halogen, cyano, or C_{1-6} alkyl optionally substituted -mono, -di or -tri halogen; and

R^6 represents carboxy or tetrazolyl.

(2) An aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:



(I-i)

wherein

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 independently represent CH or N;

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NR^{12}R^{13}$, or $-CHR^{14}R^{15}$,

wherein

R^{11} represents (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, or (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl;

R^{12} and R^{13} independently represent hydrogen, (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl,

or

R^{12} and R^{13} together form with the nitrogen atom, 5-7 membered saturated hetero ring optionally interrupted by O or NH;

R^{14} and R^{15} independently represent hydrogen, aryloxy, heteroaryloxy, (C_{1-6}) alkyl optionally substituted by aryl, heteroaryl, aryloxy, or heteroaryloxy, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl

or heteroaryl, aryl substituted (C_{1-6}) alkoxy(C_{1-6}) alkylene, or heteroaryl substituted (C_{1-6}) alkoxy(C_{1-6}) alkylene,

or

R^{14} and R^{15} together form with the CH, (C_{3-8})cycloalkyl optionally interrupted by NH, or O,

or

R^{14} and R^{15} together form with the CH, phenyl optionally substituted by hydroxy, halogen or (C_{1-6}) alkyl;

R^2 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, di(C_{1-6}) alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen,

hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^3 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^4 represents hydrogen, hydroxy, halogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino; $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaromatic ring optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^5 represents hydrogen, hydroxy, cyano, or C_{1-6} alkyl optionally substituted -mono, -di or -tri halogen; and

R^6 represents carboxy or tetrazolyl.

(3) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^6 represents carboxy.

(4) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^3 and Q^4 represent N;

Q^1, Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^6 represents carboxy.

(5) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1 and Q^4 represent N;

Q^2, Q^3, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^6 represents carboxy.

(6) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^6 represents carboxy.

(7) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1, Q^3 and Q^8 represent N;

Q^2, Q^4, Q^5, Q^6 and Q^7 represent CH; and

R^6 represents carboxy.

(8) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^3, Q^4 and Q^8 represent N;

Q^1, Q^2, Q^5, Q^6 and Q^7 represent CH; and

R^6 represents carboxy.

(9) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents aryl(C_{1-6})alkoxy, aryl(C_{1-6})alkoxy(C_{1-6})alkylene or aryl-oxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or aryl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino.

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

(10) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^3 and Q^4 represent N;

Q^1, Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents aryl(C_{1-6})alkoxy, aryl(C_{1-6})alkoxy(C_{1-6})alkylene or aryloxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or aryl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

(11) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1 and Q^4 represent N;

Q^2, Q^3, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents aryl(C_{1-6})alkoxy, aryl(C_{1-6})alkoxy(C_{1-6})alkylene or aryloxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or aryl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

(12) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein
Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents aryl(C_{1-6})alkoxy, aryl(C_{1-6})alkoxy(C_{1-6})alkylene or aryloxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or aryl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

(13) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents phenyl(C_{1-6})alkoxy, phenyl(C_{1-6})alkoxy(C_{1-6})alkylene or phenoxy(C_{1-6})alkyl; and

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

(14) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^3 and Q^4 represent N;

Q^1, Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents phenyl(C_{1-6})alkoxy, phenyl(C_{1-6})alkoxy(C_{1-6})alkylene or phenoxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

(15) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1 and Q^4 represent N;

Q^2, Q^3, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents phenyl(C_{1-6})alkoxy, phenyl(C_{1-6})alkoxy(C_{1-6})alkylene or phenoxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

(16) The aryl or heteroaryl amino alkane derivative of the formula (I-i), its tautomeric or stereoisomeric form, or a salt thereof:
wherein
Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents phenyl(C_{1-6})alkoxy, phenyl(C_{1-6})alkoxy(C_{1-6})alkylene or phenoxy(C_{1-6})alkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one or more substituents selected from the group consisting of by halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents carboxy.

(17) The aryl or heteroaryl amino alkane derivative, its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said derivative is selected from the group consisting of the following compounds:
N-{4-[4-(benzyloxy)phenyl]-2-pyrimidinyl}phenylalanine;
N-{6-[4-(Benzyloxy)phenyl]-4-pyrimidinyl}phenylalanine;
N-{4-[4-(Benzyloxy)phenyl]-2-pyrimidinyl}phenylalanine;
N-{2-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalanine; and
N-[4'-(Benzyloxy)-1,1'-biphenyl-3-yl]phenylalanine.

(18) A medicament comprising the compound, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(19) The medicament as claimed in claim 18, further comprising one or more pharmaceutically acceptable excipients.

(20) The medicament as claimed in claim 18, wherein the compound, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a PGI2 antagonist.

(21) An agent to treat or prevent a urological disorder or disease; comprising the compound, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(22) An agent to treat pain; comprising the compound, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(23) An agent to treat hypotension; comprising the compound, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(24) An agent to treat hemophilia and hemorrhage; comprising the compound, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(25) An agent to treat inflammation; comprising the compound, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(26) Use of compounds according to any of Claims 1 to 17 for manufacturing a medicament for the treatment and/or prophylaxis of urological disorders.

(27) Process for controlling urological disorders in humans and animals by administration of a PGI2-antagonisticly effective amount of at least one compound according to any of Claims 1 to 17.

aryl or heteroaryl amino alkane derivatives

ABSTRACT

The present invention relates to aryl or heteroaryl amino alkane derivatives which are useful as an active ingredient of pharmaceutical preparations. The aryl or heteroaryl amino alkanes of the present invention have PGI2 antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with PGI2 activity.

Such diseases include urological diseases or disorder as follows: bladder outlet obstruction, overactive bladder, urinary incontinence, detrusor hyper-reflexia, detrusor instability, reduced bladder capacity, frequency of micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benighn prostatic hypertrophy (BPH), prostatitis, urinary frequency, nocturia, urinary urgency, pelvic hypersensitivity, urethritis, pelvic pain syndrome, prostatodynia, cystitis, or idiophatic bladder hypersensitivity.

The compounds of the present invention are also useful for treatment of pain including, but not limited to inflammatory pain, neuropathic pain, acute pain, chronic pain, dental pain, premenstrual pain, visceral pain, headaches, and the like; hypotension;hemophilia and hemorrhage; and inflammation, since the diseases also relate to PGI2.